as a co-mitogen for lymphocyte activation, acting a stimulus for mononuclear phagocyte monokine elaboration, and possibly determining the aggressiveness of and metastatic capability of tumor cells.

Applicants have demonstrated that CD44 plays an important role in HIV-1 infection of human mononuclear phagocytes (in addition to the subject disclosure, see the manuscript by Rivadeneira et al forwarded with the December 23, 1993 Amendment). Applicants have also demonstrated that a variety of monoclonal anti-CD44 antibodies can inhibit the infection of human monocytes and tissue macrophages with monocytotropic HIV-1 strains (as well as with fresh HIV-1 clinical isolates). The inhibition is potent and highly reproducible.

In other work, Applicants have used the human T cell lymphoblastoid cell line Jurkat (a line that is CD4+ and CD44 negative) to further demonstrate the importance of CD44 in HIV-1 infection of human cells (see abstract submitted with December 23, 1993 Amendment). These studies evidence the fact that CD44H is a cellular determinant of HIV-1 infectability, and that it is especially important in determining whether a cell can be infected with a monocytotropic HIV-1 strain.

Mononuclear phagocytes (monocytes and macrophages) are important cellular targets for HIV-1. These cells can be infected *in vitro* and *in vivo*. Infected mononuclear phagocytes

in brain, bone marrow, spleen, lung, and other tissues act as reservoirs for the virus. Different viral strains of HIV-1 have the capability of infecting different cell types: generally, monocytotropic strains can infect mononuclear phagocytes, and lymphocytotropic strains infect lymphocytes and *in vitro*-cell line cells. The monocytotropic strains have been shown to be "non-syncytium inducing" (NSI) strains (thus, monocytotropic ≈ NSI), while the lymphocytotropic strains are "syncytium inducing" (SI) strains (thus, lymphocytotropic ≈ SI). The presence of SI viral strains correlates with the "stage" of HIV infection (advanced infection and AIDS stages are characterized by predominance of SI strains, while NSI strains are seen in early stages of infections). Irrespective of the relative amounts of NSI and SI strains in an infected individual, NSI strain viruses are preferentially transmitted to non-infected individuals. This may be due to an NSI strain virus preferentially infecting mononuclear phagocytes at the sites of invasion (eg, macrophages or dendritic cells in mucosal surfaces), or a lack of appropriate protective immune responses to the NSI strain viruses.

The foregoing factors underscore the importance of mononuclear phagocytes, NSI (monocytotropic) strains, and HIV-1 infection: the importance of mononuclear phagocytes as targets and reservoirs for HIV-1 infection, and the importance of

mononuclear phagocytes as initial cells of infection in the primary infection event(s). Strategies aimed at preventing infection of mononuclear phagocytes by monocytotropic (NSI) HIV-1 strains may ultimately be the most potent anti-HIV infection approach.

The present invention relates to the use of anti-CD44 antibodies, soluble CD44 ligands (eg, hyaluronic acid), or soluble CD44 for the *in vivo*, *ex vivo*, and/or topical inhibition of HIV-1 infection in humans. For *in vivo* treatment, the agents can be administered intravenously. For *ex vivo* use (see page 30 of application, last paragraph), the agent can be mixed with a potentially infected produce (eg blood, blood plasma, or purified blood factor such as coagulation factor VIII or IX) before administration to the patient. *Ex vivo* mixing would prevent infection of host cells by the administered product. For topical treatment, the agent can be administered in a solution (eg liquid or gel or foam form) within a condom or to a mucosal surface (see page 30 of the subject application, lines 20-22) (eg rectum, vagina or mouth) before sexual intercourse. So administered, this agent would prevent HIV-1 infection of the mucosal mononuclear phagocytes.

The Examiner is requested to reconsider the rejection, bearing the foregoing in mind. The Examiner is requested to note that the fact that CD44 is a determinant of HIV-1 infection is

clearly evidenced by the data presented in the application and further evidenced by the data presented in the manuscript and abstract submitted with the December 23, 1994 Amendment. The use of the word "may" in the abstract in no way negates those data. Further, the therapeutic strategies which the Examiner refers to as speculative are clearly set forth in the application (for example, at page 30). In this regard, the Examiner's attention is particularly directed to the fact that the agents to which the claims refer can be used topically, as well as otherwise. The Examiner has not given any explanation as to why the data provided would not be predictive of efficacy in such a setting.

The utility of the present invention is definite and in a currently available form. The Examiner is reminded that commercial availability is not necessary. No further showing should be necessary.

Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is respectfully requested.

Respectfully submitted,

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